CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
PUBLIC REPORT 2008-4

Active Ingredient: Mandipropamid
Tracking ID Number 221585

DESCRIPTION OF ACTION

Syngenta Crop Protection, Inc., (Syngenta) submitted an application to the Department of Pesticide Regulation (DPR) for California registration of Revus®, EPA Reg. No. 100-1254. Revus® contains the new pesticide active ingredient mandipropamid. Mandipropamid is a fungicide, and is labeled for use on a wide range of fruit and vegetable crops including broccoli, kale, onions, melons, grapes, peppers, tomatoes, and potatoes.

On January 17, 2007, Syngenta requested that DPR accept its application for California registration of Revus® concurrently with its submission of an application to the U.S. Environmental Protection Agency (U.S. EPA) for federal registration. California Food and Agricultural Code section 12836.6 allows DPR to accept applications for registration of pesticide products containing new active ingredients concurrently with the submission of an application to U.S. EPA. U.S. EPA registered Revus® conditionally on January 9, 2008. Under the federal conditions of registration, Syngenta is required to provide an acceptable chronic *Daphnia* study and storage stability data for SYN 500003, which is a metabolite of mandipropamid.

DPR evaluated the product label and the submitted data for Revus®, and found them acceptable to support conditional registration. Precautionary and first aid statements and other protective measures on the product labels adequately mitigate the potential health risks to users. The data adequately substantiates Revus® as an effective fungicide. DPR does not expect significant adverse environmental impacts to result from registration of this product.

BACKGROUND

Registrant: Syngenta
Common name: Mandipropamid
Chemical name: 2-(4-chlorophenyl)-N-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy acetamide
Brand name: Revus®
Uses: Fungicide
Pests controlled: Downy mildews, late blight, Phytophthora blight, and blue mold
Type of registration: Conditional Registration

Mandipropamid is a mandelamide fungicide, meaning that it is a member of the carboxylic acid amide (CAA) chemical class. The mode of action of mandipropamid is not fully understood. It prevents spore germination and inhibits fungus mycelial growth and sporulation. Revus® is formulated as a concentrated suspension 23.4% mandipropamid. Revus® is labeled for use on a wide range of fruit and vegetable crops including broccoli, kale, onions, melons, grapes, peppers,

tomatoes, and potatoes for control of various fungi such as downy mildews, late blight, Phytophthora blight, and blue mold. The product label for Revus® recommends use of the product as part of an integrated pest management (IPM) program.

SCIENTIFIC REVIEW

A. Chemistry

Syngenta submitted chemistry studies from two products: Revus®, which contains 23.4% mandipropamid and Mandipropamid Technical containing 96% mandipropamid. DPR evaluated the submitted studies, and determined that the product chemistry and environmental fate data support conditional registration of Revus®. Conditional registration is contingent upon the submission of an acceptable one-year storage stability study for Revus®. Syngenta did not submit food and animal feed residue data for Revus®. In accordance with California Notice 2004-7, DPR no longer requires these data.

1. Product Chemistry**:** The product chemistry results are summarized in Table 1.

Table 1. Physical and Chemical Properties of Mandipropamid

Properties	Values
Physical state	Light beige powder no odor
Bulk density	1.24 grams (g)/centimeter^3 (cm)
Molecular weight	383.59 g/mol
pH (1% dispersion)	7.1
Melting point	96.4 – 97.3° C
Solubility	Soluble in acetone, dichloromethane, ethyl acetate
Water solubility	4.2 ppm @ 25° C
Vapor pressure	$<7.1 \times 10^{-9}$ @ 25° C
Dissociation constant (pKa)	No ionization in H_2O, pH 1.9 – 9.8
Henry's Law	$<9.1 \times 10^{-10}$ atm·m^3/mol @ 25° C
K_{ow}	1,600 @ 25° C
Storage stability and corrosion (technical material)	Stabile and non corrosive to packaging

2. Environmental Fate**:** The mandipropamid environmental fate data were derived from Mandipropamid Technical. The studies included hydrolysis, aquatic and soil photolysis, soil adsorption/desorption, aerobic and anaerobic soil metabolism, terrestrial field dissipation and soil storage stability. DPR found the studies to be satisfactory. It must be noted that when compared with the U.S. EPA and California EPA criteria for predicting the potential of a

chemical to reach ground water, the submitted studies indicated that mandipropamid has the potential to leach, as summarized in Table 2. Due to this concern, Revus® was routed to the Environmental Monitoring Branch for review. However, after further review, based on a combination of factors, including foliar application, use rate, and physical-chemical properties, DPR determined that use of Revus® fungicide would result in a low potential to contaminate California ground water. The submitted product chemistry, residue chemistry, and environmental fate data support registration of Revus®.

Table 2. Comparison of U.S. EPA and Cal/EPA Ground Water Leaching Criteria with Environmental Fate Study Results for Mandipropamid

Parameter	**Potential to Leach Value** (U.S. EPA)	**Potential to Leach Value** (Cal/EPA)	**Experimental Value**	**Criteria Exceeded**
Water solubility	> 30 parts per million (ppm)	> 3 ppm	4.2 ppm	No/Yes
Soil adsorption coefficient (K_d)	< 5 milliliter (ml)/gram (g)		2.88 – 53.2	Yes
K_{oc}		<1,900 ml/g	405 - 1290 ml/g	Yes
Hydrolytic half-life	> 30 days	> 14 days	Stable	Yes
Photolytic half-life	> 7 days		1.3 - stable	Yes
Anaerobic soil metabolic half-life	> 21 days	> 9 days	155 – 182 days	Yes
Aerobic soil metabolic half-life	> 21 days	> 610 days	26.2 – 72.0 days	Yes/No
Field dissipation half-life	> 21 days		75.6 – 169 days	Yes

B. Toxicology

Syngenta submitted adequate toxicology studies to conduct a complete toxicological evaluation of Revus®. DPR evaluated the submitted data to determine the potential for adverse health effects. The product labels adequately identify the potential acute toxicity hazards indicated by the data reviewed. The first aid statements and personal protective equipment (PPE) requirements are adequate for the indicated acute toxicity hazards. The restricted entry interval of 4 hours is adequate for the indicated acute toxicity hazards. The two submitted dermal sensitization studies derived from the technical material are unacceptable because of the weak positive control response that was observed. No adverse effects were observed in these studies, and they are possibly upgradeable. The dermal sensitization study conducted on the formulated product indicated that the product was not a dermal sensitizer. The acute toxicity parameters for mandipropamid are summarized in Table 3.

Table 3. Summary of Acute Toxicity of Mandipropamid*

Type of Study	Acute Toxicity Values**	Acute Toxicity Category
Acute oral	LD_{50} > 5000 milligrams (mg)/kilograms (kg)	IV
Acute dermal	LD_{50} > 5050 mg/kg	IV
Acute inhalation	LC_{50} > 5.19 mg/l	IV
Primary eye irritation	N/A	IV
Primary dermal irritation	N/A	IV
Dermal sensitization technical	N/A	Inconclusive
Dermal sensitization Revus®	N/A	Non Sensitizer
Acute neurotoxicity	N/A	No adverse effects
Signal word	N/A	No signal word required

* Toxicity testing was conducted with Mandipropamid Technical containing 96.5% active ingredient.
**Acute Toxicity Values expressed as:
LD_{50} = Lethal dose that kills 50% of the test population
LC_{50} = Lethal environmental concentration that kills 50% of the test population
N/A = Not applicable

DPR found the submitted subchronic and chronic toxicology studies for mandipropamid sufficient to satisfy the data requirements of the Birth Defects Prevention Act (Food and Agricultural Code section 13121, et al.). DPR did not identify possible adverse effects in any of the submitted studies.

DPR prioritizes pesticide active ingredients for risk assessment based on the nature of the potential adverse health effects, the number of potential adverse effects, the number of species affected, no observable effect levels (NOELs), the potential for human exposure, use patterns, and other similar factors. Based on these criteria, pesticides with the greatest potential for health problems are placed in high priority, with other chemicals being in moderate or low priority. DPR has not prioritized mandipropamid for risk assessment at this time. The purpose of the risk assessment would be to appraise the potential for mandipropamid to cause adverse health effects in humans if exposed to the pesticide through legal use. A summary of all mandipropamid toxicology data is available on DPR's website at:
http://www.cdpr.ca.gov/docs/risk/toxsums/pdfs/5961.pdf.

C. Health & Safety

DPR compared the medical management information and PPE requirements of the Revus® label to the acute toxicity study results. DPR found that the product label bears all required statements and warnings regarding safety to handlers and other persons who may be exposed to the pesticide. The product label bears adequate First Aid statements and the PPE requirements are adequate for the indicated acute toxicity hazards. The label contains a restricted entry interval (REI) warning prohibiting worker entry into treated areas for 4 hours after application. In addition, the product label requires users to wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.

D. Efficacy & Phytotoxicity

Revus® is formulated as a concentrated suspension containing 23.4% mandipropamid. Revus® is intended for use on brassica vegetables, bulb vegetables, fruiting vegetables, grapes, leafy vegetables, potatoes, tomatoes, and tuberous and corm vegetables to control the following fungi, downy mildew, Phytophthora blight, late blight, and blue mold. The Revus® label recommends use rates ranging from 5.5 – 8.0 ounces of product per acre applied by ground or aerial spray equipment or via chemigation.

Syngenta submitted efficacy and phytotoxicity data for Revus®. The submitted data were developed in California, Georgia, Michigan, Texas, New York, and Florida. Mandipropamid was tested against downy mildew, Phytophthora, late blight, and blue mold on label representative crops. The application rates and methods used were consistent with the use directions on the Revus® label. No signs of phytotoxicity were observed in any of the treated crops. The Revus® label contains a section titled “Resistance Management” that provides suggestions for the use of Revus® in integrated pest management (IPM) programs. The product label also contains directions for jar testing to determine compatibility of Revus® with other products. DPR determined that when used as directed mandipropamid is not phytotoxic and is effective as a fungicide for its labeled uses.

E. Fish & Wildlife

The registrant submitted fish and wildlife toxicity studies, including studies on *Daphnia magna*, eastern oyster, mysid shrimp, rainbow trout, sheepshead minnow, flathead minnow, bobwhite quail, mallard duck, earthworms, and honeybee. The submitted data are adequate to characterize mandipropamid toxicity to wildlife and aquatic animals from an environmental exposure**.** The results of these studies are summarized in Table 4 on page 6.

Table 4. Summary of Fish & Wildlife Toxicity Values*

Test Animal	Type of Study	Acute Toxicity Value**	Relative Toxicity
Daphnia magna	Water exposure (48 hrs)	71.0 mg/l EC_{50}	Slightly toxic
Daphnia magna	Reproduction study (21 day)	0.87 mg/l NOEC 0.87 mg/l LOEC	N/A
Eastern oyster	Water exposure (96 hrs)	0.97 mg/l EC_{50}	Highly toxic
Mysid shrimp	Water exposure (96 hrs)	1.7 mg/l LC_{50}	Moderately toxic
Rainbow trout	Water exposure (96 hrs)	4.4 mg/l LC_{50}	Moderately toxic
Sheepshead minnow	Water exposure (96 hrs)	4.5 mg/l LC_{50}	Moderately toxic
Flathead minnow	Water exposure (96 hrs)	>5.8 mg/l LC_{50}	Moderately toxic
Flathead minnow	Life stage toxicity (32 day)	0.50 mg/l NOEC	N/A
Bobwhite quail	Acute oral dose	>2250 mg/kg LD_{50}	Relatively non-toxic
Bobwhite quail	Feeding (5 day)	>5620 ppm LC_{50}	Relatively non-toxic
Bobwhite quail	Reproduction study (20 weeks)	1000 ppm NOEC	N/A
Mallard duck	Acute oral dose	>1000 mg/kg LD_{50}	Slightly toxic
Mallard duck	Feeding (5 day)	>5620 ppm LC_{50}	Relatively non-toxic
Mallard duck	Reproduction study (20 weeks)	1000 ppm NOEC	N/A
Earthworm	Acute toxicity (14 day)	>1000 mg/kg LC_{50}	Practically non-toxic
Honeybee	Acute oral toxicity (48 hrs)	>200 micrograms (µg)/bee LC_{50}	Slightly toxic
Honeybee	Acute contact toxicity (48 hrs)	>200 µg/bee LC_{50}	Slightly toxic

* The test substance used for the studies was the technical active ingredient.

** Acute Toxicity Values expressed as:
LD_{50} = Lethal dose that kills 50% of the test population
LC_{50} = Lethal environmental concentration that kills 50% of the test population
EC_{50} = Concentration of a toxicant causing a defined non-lethal effect in 50% of the test population
NOEC = No observed effect concentration
LOEC = Lowest observed effect concentration

The data indicate that mandipropamid is practically non-toxic to earthworms, slightly toxic to birds, *Daphnia,* and honeybees, moderately toxic to fish and mysid shrimp, and highly toxic to eastern oyster. To mitigate the hazards to aquatic organisms, the Environmental Hazards statement on the Revus® label contains the following warning statement:

> Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwater or rinsate.

When used as directed, DPR does not expect mandipropamid to be released into soil or waterways.

ALTERNATIVES

Revus® is a new mandelamide fungicide which shows effectiveness against foliar infecting fungi including downy mildew in grapes and late blight in potatoes and tomatoes. Upon application, mandipropamid locks tightly to the waxy cuticle of treated leaves, quickly becoming rainfast and establishing a protective barrier to prevent fungi infection. Mandipropamid has very low mammalian toxicity and is classified by U.S. EPA as a reduced risk pesticide. The Revus® labels recommend use of the products as part of an integrated pest management (IPM) program. A number of other active ingredients are registered as broad-spectrum fungicides for use on turf and fruits and vegetable crops. However, an effective integrated pest management strategy requires the flexibility of a large number of comparable, but not exactly equivalent, pesticides in order to reduce the development of resistance.

CONCLUSION

DPR evaluated the product label and scientific data submitted to support the registration of Revus®. The label and data were found acceptable to support conditional registration of Revus®. The acute health risks to humans from exposure to mandipropamid are minimal due to its low mammalian toxicity. The precautionary and first aid statements on the product label, and the recommended protective measures mitigate potential health risks to persons who may be exposed to these pesticides. If a risk assessment conducted by DPR determines that exposure to mandipropamid may result in unacceptable margins of exposure, further restrictions will be placed on the use of mandipropamid at that time. DPR recommend conditional registration of Revus® for one year contingent upon the submission of an acceptable one-year storage stability study. If the registrant does not submit the required data within one year, the registration of Revus® will not be renewed.